

REMARKS

Claims 1-38 are pending in the application. Claims 33-38 have been withdrawn. Claims 1, 3, 4, 5, 6, 10, 11, 12, 13, and 30 have been amended and new claim 39 has been added. Support for the claim amendments may be found throughout the specification, including the claims as originally filed. No new matter has been added to the specification or claims.

Support for the amendments in claim 1 may be found, for example, on page 2, lines 22-26.

Support for the phrase “corresponding to” in claims 3, 4 and 6 may be found, for example, on page 5, lines 4-13 as well as in original claims 1, 5 and 11.

Amendment to claim 5 has been made to correct the typographical error.

Support for the amendments in claim 11 may be found, for example, on page 5, pages 10-13, page 27, lines 12-31, and pages 28-29.

Support for the amendments in claims 10 and 13 may be found, for example, on page 16, lines 27-29 and page 19-27.

Support for the amendments in claim 12 may be found, for example, on pages 19-20.

Support for the amendments in claim 30 may be found, for example, on pages 9-10.

Support for new claim 39 may be found, for example, on page 19, lines 9-21.

The amendments to the claims are being made solely to expedite prosecution of the present application and should in no way be construed as an acquiescence to any of the Examiner’s rejections. Applicants reserve the right to further prosecute claims drawn to all subject matter disclosed in the instant patent application or in a continuation hereof.

Amendments to the specification on page 28, lines 1-2, have been made to address the Examiner’s objection. Amendments to the specification on page 1, lines 1-5 have been made to incorporate the NIH grant number. No new matter has been added by these amendments.

The Examiner’s remarks in the last Office Action are addressed below. It is believed that the amended claims and all dependent claims, taken in light of the remarks made herein, meet all criteria for patentability.

RESTRICTION/ELECTION REQUIREMENT

In response to the Restriction Requirement, Applicants reaffirm the telephonic provisional election, with traverse, of Group I, claims 1-32 drawn to a method of analyzing a cell with a biomarker.

CLAIM REJECTIONS

Rejection of claims under 35 U.S.C. §112, first paragraph

Enablement

The Examiner has rejected claims 11-29 contending that “[t]he claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention”. Specifically, the Examiner contends that “absent is the intended goal that would be achieved through the implementation of the instantly claimed method” because “ 1) no output information is identified; 2) if an output is information is derived what is the output information intended to represent/what does one do with the output information?”.

In order to expedite prosecution and not in acquiescence to the rejections, Applicants have amended claim 11 and its dependent claims thereon to specify that the method is for localizing a biomarker within a sub-cellular compartment of a cell. For support, Applicants direct the Examiner to page 5, lines 14-30 and page 6, lines 1-9 of the specification. As disclosed, the use of methods as taught in the presently claimed invention allows the accurate assignment of a biomarker to a sub-cellular compartment. The expression of a biomarker within a particular subcellular compartment (e.g. the presence of beta-catenin within the nucleus as opposed to the cytoplasm) may be useful diagnostically (e.g. to identify patients who have a particular disease (for example, detection of beta-catenin in the nucleus of a subject is an indicator of carcinogenesis), have been exposed to a particular toxin or are responding well to a particular therapeutic or organ transplant) or prognostically (e.g. to identify patients who are likely to develop a particular disease, respond well to a particular therapeutic or be accepting of a particular organ transplant) (page 3, lines 4-11).

As amended, Applicants believe that claim 11 and claims dependent thereon obviate the rejection. Applicants, therefore respectfully request that the rejection be reconsidered and withdrawn.

Rejection of claims under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 3, 4, and 6 “as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.” Specifically, claims 3, 4, and 6 have been rejected for reciting the term “associated,” which the Examiner contends is “vague and indefinite.”

In order to expedite prosecution and not in acquiescence to the rejection, Applicants have amended claims 3, 4, and 6 to replace the term “associated” with the phrase “corresponding to”, as it appears in non-rejected claim 1, 5 and 11.

As a result of these amendments, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejection of claims under 35 U.S.C. §102(b) over Bacus et al.

The Examiner has rejected claims 1-13 and 30-32 under 35 U.S.C. §102(b) as being anticipated by Bacus et al. (U.S. Patent Number 4,998,284). The Examiner contends that Bacus et al. as teaches “a method and apparatus for use in performing automated classification of cell and other microscopic specimens.” Specifically, the Examiner asserts that “[t]he apparatus and techniques provide: 1) alternative staining and analytical techniques for different cells, cytoplasms, and cell populations; 2) enhance image and color separation for greater distinguishment by the image processing equipment.”

To anticipate a claim, a reference must teach each and every element of the claim. However, Bacus et al., fails to teach or suggest the instant claimed methods for identifying where within a cell a particular biomarker is localized. As described in claim 1 (and claims 2-10, which

depend from claim 1), Applicant's novel process involves obtaining two different images of a cell, one image of a sub-cellular compartment (e.g. nucleus or cytoplasm) and the other of a biomarker (e.g. a nucleic acid or protein) and superimposing the images to localize the biomarker within a sub-cellular compartment.

As further specified by independent claim 11 and claims 12-29, which depend from claim 11, Applicant's process can involve the following steps:

- a) obtaining a first image of a cell treated with a first stain that is selective for a first sub-cellular compartment within the cell and a second stain that is selective for at least one biomarker;
- b) determining an intensity value for the first stain at a plurality of pixel locations in the first image;
- c) based on the intensity values, determining pixel locations in the first image that correspond to the first sub-cellular compartment within the cell and assigning those pixel locations to the first sub-cellular compartment;
- d) obtaining a second image of the cell and determining an intensity value for the second stain at a plurality of pixel locations in the second image; and
- e) comparing the first and second images, wherein the presence of pixel locations in the second image that are within the first sub-cellular compartment indicate that the biomarker is within the first sub-cellular compartment.

In contrast to the instant claimed invention, Bacus et al., purports to teach "an improved apparatus for the measurement of cell object features, such as morphology and mass, and a methodology to enhance cell structures for quantitative measurement methods utilizing this apparatus." (col. 1, lines 25-29). This apparatus is said to provide "a dual filtering method to distinguish areas stained by red chromogen (cytoplasm) and the areas stained by the blue Thionin (DNA)" (see col. 12, lines 30-46). The Examiner contends that Bacus et al., teaches that this apparatus "combines [emphasis added] the two filtered images to mark the selected cells on [an] image monitor while displaying the nuclear DNA area."

Although the Bacus patent may teach a method for simultaneously imaging a cell stained with multiple stains, the Bacus patent does not teach or suggest Applicant's novel process of superimposing an image of a biomarker and a sub-cellular compartment to determine if the biomarker is contained within the sub-cellular compartment.

In addition, Bacus et al. does not teach or suggest a method for localizing a biomarker within a sub-cellular compartment of a cell using intensity values and pixel locations, as required by independent claim 11 as amended and its dependent claims 12 and 13. Bacus et al also does not teach a method of analyzing a cell containing sample by obtaining an adjusted intensity value, as required by independent claim 30 and its dependent claims 31 and 32. This reference also does not teach methods of subtracting out-of-focus elements as required by claims 7, 8, 30, 31 and 32.

Accordingly, because Bacus et al. (U.S. Patent Number 4,998,284) does not teach each and every element of claims 1-13 and 30-32, Applicants respectfully request reconsideration and withdrawal of these rejections under 35 U.S.C. §102(b).

Rejection of claims under 35 U.S.C. §103

The Examiner has rejected claims 1-32 under 35 U.S.C. §103 (a) as being obvious over Bacus et al. (U.S. Patent Number 4,998,284) in view of Garini et al. (U.S. Patent Number 6,165,734).

The Examiner relies on Bacus et al. as described above. The Examiner further relies on Garini et al. as teaching "multiple staining". Based on these teachings, the Examiner states that "[o]ne would be motivated to characterize/identify other cellular components (i.e. nuclear, membrane, etc.) with the cell image as indicated by Bacus et al.

In order to render a claimed invention obvious, the combined teachings of prior art references must disclose or suggest **all** elements of the invention, or motivate a person skilled in the art to modify the reference teachings so as to arrive at the claimed invention.

Applicants urge that the combined teachings of Bacus et al. (U.S. Patent Number 4,998,284) and Garini et al. (U.S. Patent Number 6,165,734) do not form a prima facie case of obviousness as Garini et al. (U.S. Patent Number 6,165,734) does not supply the limitations of the claims that are not taught by Bacus et al. (U.S. Patent Number 4,998,284). Applicant assert that Garini et al. is devoid of any teaching, suggestion, motivation, or guidance for superimposing two images to localize a biomarker within a defined area, as required by independent claim 1 as amended, a method for localizing a biomarker in a cell containing sample using intensity values and pixel locations, as required by independent claim 11 as amended or a method of analyzing a cell containing sample by obtaining an adjusted intensity value, as required by independent claim 30.

As such, Applicants respectfully submit that the claimed invention cannot be deemed obvious in light of the combined teachings of these two references. Applicants respectfully request the withdrawal of the rejection of claims 1-32 under 35 U.S.C. §103 (a).

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims now pending are in condition for allowance, and notification of such is respectfully requested.

The Commissioner is hereby authorized to credit any overpayment or charge any deficiencies to Deposit Account Number **06-1448, Reference YUA-001.01**.

If, for any reason, a telephonic conference with the Applicant would be helpful in expediting prosecution of the instant application, the Examiner is invited to call Applicants' Agent at the telephone number provided below.

Respectfully submitted,
FOLEY HOAG LLP

A handwritten signature in black ink, appearing to read 'Beth E. Arnold', written over a horizontal line.

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